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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/277,064	03/26/1999	LINDA A. SHERMAN	TSRI.433.1-D	3058

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/277,064	SHERMAN, LINDA A.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 61-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 61-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant adds new claims 61-75 that are related to claim 1 and are not new matter.

Accordingly, claims 1, 61-75 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Rejection under 35 USC 112, first paragraph of claim 1, pertaining to lack of enablement for a method for specifically activating cytotoxic T lymphocytes in vivo in an animal having malignant cells that express a Her-1/Neu protein, remains for reasons already of record in paper of 07/12/04.

New claims 61-75 are rejected pertaining to lack of enablement for a method for treating a patient having a "tumor", that expresses a Her-2/Neu protein, for the same reasons.

Applicant argues that the Examiner requires a working example to be provided that demonstrates a particular level or efficacy of the claimed invention.

This is not found to be persuasive. The Examiner did not require a working example to be provided that demonstrates a "particular level of treatment" in the claimed invention.

Further, although an example showing the efficacy of the encompassed method of treating cancer expressing Her-2/neu, or of specifically activating cytotoxic T lymphocytes in human patient having Her-2/neu malignant or cancer cells, wherein said cytotoxic T cells are effective in killing cancer cells *in vivo*, is not required, however, given:

1) the unpredictability of treating cancer, and in particular the unpredictability of killing target malignant cells by T cells specific for SEQ ID NO:12 in patients with cancer burden and having Her-2/neu as self antigen,

2) the lack of correlation between production of specific T cells in transgenic mouse that is cancer free and does not express the particular human Her-2/neu peptide of SEQ ID NO:12 as self antigen and the production of T cells that could kill target cancer cells in patients having cancer burden and having Her-2/neu as self antigen, and

3) the lack of correlation between killing cancer cells in vitro and killing primary cancer cells in vivo, and in addition,

4) the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that

information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

A. The breadth of the claims and nature of the invention

Applicant argues that the claimed invention entails administration of a polypeptide which is fully disclosed in the specification. Applicant argues that the specification further discloses a working example of the step of immunizing an animal with the polypeptide of SEQ ID NO:12.

The arguments are deemed not to be persuasive. **The scope of the claims is overly broad, encompassing a method for treating or specifically activating cytotoxic T lymphocytes in cancer patients with tumor burden, and having "Her-2/ Neu comprising SEQ ID NO:12 as self-antigen"**, wherein said CTLs specifically kill target malignant cells that express a Her-2/Neu protein of said patients, comprising administering the peptide of SEQ ID NO:12.

The specification however only discloses activating cytotoxic T lymphocytes in **transgenic mouse that is cancer free**, by administering the Her-2/Neu peptide of SEQ ID NO:12. **Further SEQ ID NO:12 is from human, and the specification does not disclose that said particular human peptide has the same structure as the**

corresponding Her-2 /neu peptide in the transgenic mice. Further, **the specification only discloses that said cytotoxic T lymphocytes could kill cancer cells line expressing Her-2/Neu "in vitro", which cannot be correlated with in vivo conditions**.

B) The State of the Art and the Level of Skill in the Art

Applicant argues that the step of immunizing an animal with a polypeptide was routine in the art.

The Examiner takes note that although the step of immunizing a peptide is routine in the art, it is not known in the art that the specific human peptide of SEQ ID NO:12 from Her-2/Neu protein could specifically activate cytotoxic T lymphocytes in cancer patients with tumor burden, such as human cancer patients, having as self-antigen a Her-2/ Neu protein comprising said peptide, wherein said CTLs specifically kill target malignant cells that express a Her-2/Neu protein of said patients.

C) The level of predictability in the Art

Applicant argues that the Examiner requires a working example to be provided that demonstrates a particular level or efficacy of the claimed invention.

Applicant argues that Sherman et al does not teach that self-tolerance will occur for every peptide used as immunogens. Applicant argues that self-tolerance does not eliminate the CTL response for all immunogens expressed at low levels by normal tissues as evidenced by Sherman et al.

Applicant further argues that Sherman et al (p.47, column 2, lines 4-16) teach that Her-1/neu is expressed at low levels in normal tissue of A2.1/K^b transgenic mice.

Applicant asserts that the present specification teaches that immunization of A2.1/K^b transgenic mice with SEQ ID NO:12 specifically activates CTLs in vivo, wherein these CTLs isolated from the immunized mice specifically target malignant cells that express the Her-2/Neu protein in vitro. Applicant asserts that thus self-tolerance does not eliminate the activated CTLs response to the immunogen SEQ ID NO:12 in vivo.

Concerning the Examiner assertion that it is unpredictable that mice having tumors that express Her-2/Neu would produce CTLs specific for SEQ ID NO:12 with high affinity, Applicant asserts that the claims do not recite the asserted element.

Applicant asserts that the tumor cell lines used for cell killing assays are a suitable model system for the correlation of in vitro results to in vivo conditions.

Concerning the Examiner assertion that the expression of Her-2/Neu could be lost in a tumor, due to autochthonous immune response, Applicant asserts that the Examiner fails to provide evidence that autochthonous immune response does occur, or that the response occurs in all individuals and tumors. Applicant asserts that further, the invention is not directed to cells that do not express a Her-2/Neu protein.

Concerning the Examiner assertion that in vitro, tumor cells are continuously exposed to CTLs and cytokines, which is not the case in vivo, Applicant asserts that the Examiner never provides evidence that this alleged difference of continuous exposure to CTLS and cytokines renders the in vitro targeting of malignant,cells that express a Her-2/Neu protein an irrelevant model system, or working example, for the targeting of malignant cells that express a Her-2/Neu protein in vivo. Applicant argues that for example, the Examiner never provides evidence that tumor cells in vivo are not also

continuously exposed to CTLS and cytokines after immunization with the polypeptide of SEQ ID NO:10.

Concerning the Examiner assertion that even if activated CTLS are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells, Applicant argues that the claimed invention, as amended, is directed to those tumors that do express Her-2/Neu protein in vivo.

Applicant's arguments set forth in paper of 11/16/04 have been considered but are not deemed to be persuasive for the following reasons:

The level of unpredictability is very high in the instant application, due to:

1) **the unpredictability of self-tolerance for different peptides, resulting in unpredictable, various responses, from non-production of CTL response to production of T cells with low or varying degree of affinity**, as taught by Sherman et al, p.52, first column, and second column, first paragraph, of record.

More specifically, contrary to Applicant assertion, since Sherman et al teach that self-tolerance varies for different epitopes, one cannot predict that the particular human SEQ ID NO:12 epitope of the Her-2/neu protein of the claimed invention would not elicit self-tolerance in patients, for example, human patients, which express human Her-2/neu as self-antigen.

2) the well known immune tolerance and suppression phenomena in cancer as taught by Boon et al, of record, resulting in T cell anergy, and as disclosed in the specification (p.101), and

3) the unpredictability of sufficient numbers of Her-2/neu molecules on cancer cells surface in patients, necessary for recognition and killing by T cells, due to antigen downregulation, as taught by Cheever et al, of record, or due to inconsistencies in antigen expression or presentation by tumor cells, as taught by Boon et al, of record.

In other words, although the claims now are directed to an animal or a patient having tumor or malignant cells that express a Her-2/neu protein, one cannot predict that there are sufficient numbers of Her-2/neu molecules on cancer cells surface, necessary for recognition and killing by T cells, in an animal or a patient having tumor or malignant cells that express a Her-2/neu protein.

4) Further, in vitro killing of cancer cell lines expressing Her-2/Neu cannot be correlated with the in vivo killing of malignant cells by specific T cells, because the expression of antigens of cancer cells in culture cannot not be compared with those of primary cancer cells, due to cell culture artifact, based on the teaching of Freshney and Dermer, and because in vitro assay cannot be correlated with in vivo conditions.

Concerning Applicant assertion that the claims do not recite the asserted element, i.e. CTLs specific for SEQ ID NO:12 with high affinity, it is noted that the issue is the unpredictability of which reponse that the particular human peptide of SEQ ID NO:12 produces in patients that express Her-2/neu comprising SEQ ID NO:2 as self-antigen, wherein said response is unpredictable, varying from non-production of CTL response to production of T cells with low or varying degree of affinity, as taught by Sherman et al, p.52, first column, and second column, first paragraph, of record.

Concerning Applicant's assertion that the tumor cell lines used for cell killing assays are a suitable model system for the correlation of in vitro results to in vivo conditions, this assertion is not supported by any references. On the contrary, the art teach that dué to culture artifact, the expression of antigens of cancer cell lines could not be compared with those of primary cancer cells, due to cell culture artifact (Freshney and Dermer, of record). Further, in vivo and in vitro conditions are different, such as continuous exposure to CTLs and cytokines in in vitro assay, which is not the case in vivo. It is noted that adequate exposure of CTLs and cytokines to the target site cannot be predicted, for example it may be delayed or inadequate. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The CTLs and cytokines may not adequately reach the target because of their inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the CTLs and cytokine have no effect, and circulation into the target area may be insufficient to carry the CTLs and cytokines, and a large enough local concentration may not be established. Thus in vivo killing of primary malignant cells by specific T cells cannot be compared to in vitro killing of cancer cell lines expressing Her-2/Neu.

Concerning Applicant's assertion that the Examiner fails to provide evidence that autochthonous immune response does occur, or that the response occurs in all individuals and tumors, it is noted since it is well known that the expression of Her-2/neu could be down-regulated in cancer cells, as taught by Cheever et al, one cannot predict whether the malignant cells in the claimed invention would not have down regulation of

Her-2/neu expression on the cell surface, resulting in unpredictable numbers of Her-2/neu molecules on cell surface. Thus one cannot predict that primary malignant cells would have adequate numbers of Her-2/neu on cell surface, necessary for malignant cell recognition and killing by T cells, especially in view that the claims are not even drawn to malignant or tumor cells that "overexpress" Her-2/neu on cell surface.

Further, concerning Applicant's assertion that the invention is not directed to cells that do not express a Her-2/Neu protein, it is noted that due to antigen downregulation, as taught by Cheever et al, of record, or due to inconsistencies in antigen expression or presentation by tumor cells, as taught by Boon et al, of record, one cannot predict that the targeted malignant cells in the claimed invention would have sufficient numbers of Her-2/neu molecules on cancer cells surface in patients, necessary for recognition and killing by T cells.

In view of the above, one cannot predict that the claimed method would be successful in treating or killing malignant cells in vivo in cancer patients that express Her-2/neu comprising SEQ ID NO:12 as self antigen.

D) The amount of direction provided by the Inventor

Applicant argues that the specification discloses how to make the polypeptide of SEQ ID NO:12, and how to immunize animals with said polypeptide. Applicant argues that the specification discloses that CTLs are activated by immunization, and that the collected activated CTLs target malignant cells that express a Her-2/neu protein in vitro.

This is deemed not to be persuasive. The specification discloses activating cytotoxic T lymphocytes in transgenic mouse that is cancer free, and that does not

express the human Her-2/Neu comprising SEQ ID NO:12 as self antigen in normal tissues. The specification further discloses that said cytotoxic T lymphocytes could kill cancer cells line expressing Her-2/Neu in vitro, which could not be correlated with in vivo conditions.

The example provided by the specification cannot be correlated with successful production of specific T cells in patients with cancer burden, and having Her-2/neu comprising SEQ ID NO:12 as self antigen, wherein said T cells could successfully kill malignant cells in said patients, for reasons set forth above.

The specification provides insufficient guidance with regard to the issues discussed above and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success.

E-F) The Existence of working examples and the Quantity of experimentation needed..

Applicant argues that MPEP 2164.02 teaches that in vitro or in vivo animal model example constitutes a working example if that example "correlates" with a disclosed or claimed method, and further teach that there is no requirement of a working example. Applicant argues that the use of tumor cell lines was an accepted model system for testing anti-cancer agents commonly used by the National Cancer Institute, as shown in *In re Brana*.

Applicant argues the experimentation needed to immunize an animal having malignant cells that express a Her-2/neu protein with SEQ ID NO:10 does not even rise to the level of being complex,in view of the teaching in the specification.

The recitation of MPEP 2164.02 and *In re Brana* is acknowledged.

The arguments are deemed not to be persuasive.

It is noted that MPEP 2164.03, supra, teaches that if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Thus, although an example is not always required, however, given 1) the unpredictability of killing target malignant cells by T cells specific for SEQ ID NO:12 in patients with cancer burden and having Her-2/neu comprising the human peptide of SEQ ID NO:12 as self antigen, for reasons set forth above, 2) the lack of correlation between production of specific T cells in transgenic mouse that is cancer free and does not express Her-2/neu comprising the human peptide of SEQ ID NO:12 as self antigen and the production of T cells that could kill target cancer cells in patients having cancer burden and having Her-2/neu as self antigen, for reasons set forth above, and 3) the lack of correlation between killing cancer cells in vitro and killing primary cancer cells in vivo, for reasons set forth above, and in addition, 4) the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

In addition, new claims 61-75, drawn to a method for treating a patient having a "tumor", wherein cells of said tumor express a Her-2/neu protein encompasses a method for treating a patient having any swelling, or growth, or enlargement of tissue, such as splenitis, adipose, etc.., wherein cells of said tissue express a Her-2/neu protein, (Stedman's medical dictionary, 25th ed, 1990, pages 1652-1653) . The specification does not teach how to treat such tumor.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS

February 05, 2005

SUSAN UNGAR, PH.D
PRIMARY EXAMINER